UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/520,130 | 03/07/2000 | Robert Arathoon | P1099R2 | 1353 |

25213 7590 10/05/2007

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

| EXAMINER | |
|---|---|
| HOLLERAN, ANNE L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/05/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/520,130 | ARATHOON ET AL. | |
| | Examiner | Art Unit | |
| | Anne L. Holleran | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *54-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/10/2007 has been entered.

2. The amendment filed 8/10/2007 is acknowledged. Claims 47-53 were canceled. Claims 64-69 were added. Claims 54-69 are examined on the merits.

***Claim Rejections Withdrawn:***

### *Claim Rejections - 35 USC § 112*

3. The rejection of claim 53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment canceling claim 53.

### *Claim Rejections - 35 USC § 102*

4. The rejection of claims 47, 52, and 53 under 35 U.S.C. 102(b) as being anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994; cited in IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS) is withdrawn in view of the amendment canceling claims 47, 52 and 53.

5. The rejection of claims 47, 48, 50, 52, and 53 under 35 U.S.C. 102(b) as being anticipated by de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) is withdrawn in view of the amendment canceling claims 47, 48, 40, 52 and 53.

***Claim Rejections Maintained:***

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 54-69 remain/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 56-77 of copending Application No. 09/373,403. The rejection is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

7. Claims 54-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of US Patent No. 7,183,076. This rejection was originally a provisional rejection over application no. 10/143,437. The grounds of rejection is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

***New Grounds of Rejection:***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 54-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 is indefinite because of the phrase "a $C_H3$ region of an antibody constant domain". It is not clear if this refers to a region within the $C_H3$ domain of an antibody constant region, or if it refers to an entire $C_H3$ domain.

Claim 59 is indefinite because it recites a "A bispecific antibody comprising a first polypeptide and a second polypeptide, ..." and then also "the bispecific antibody comprising:", and then list at least three polypeptides. It would be clearer if the claim read as follows: " A bispecific antibody comprising:...", and in elements (b) and (c) "the first polypeptide" and "the second polypeptide, respectively, were amended to "a first polypeptide" and "a second polypeptide", respectively.

Claim 64 is indefinite because of the phrase "and a third and a fourth of said polypeptides are common light chains". Even though the phrase "common light chains" is present in the claims, it is not clear if each of these chains is the same or different, because they are referred to in the plural. On page 22 of the specification, the phrase "common light chain" is defined as referring to "*the* amino acid sequence of *the* light chain in the multispecific antibody" of the invention. A suggestion for amending the claims is an amendment that clearly sets forth that the third and fourth polypeptides have identical sequences.

Claim 64 is indefinite because of the phrases "heavy chain constant domain" and "heavy chain variable domain". It is not clear if these phrase refer to domains within a heavy chain constant region and with a heavy chain variable region, respectively, or if the phrases refer to the entire heavy chain constant region and heavy chain variable region, respectively.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 64, 65 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Kostelny (Kostelny, S.A., The Journal of Immunology, 148: 1547-1553, 1992; cited in the IDS).

Claim 64 is drawn to a bispecific antibody comprising four polypeptides wherein the first and the second of the polypeptides each comprises a heavy chain constant domain and a heavy

chain variable domain. Claim 64 may be interpreted as including within its scope antibodies where the light chains are not identical (see 112, 2nd rejection above). Claim 65 recites a multimerization domain in addition to a heavy chain constant domain. Claim 69 is a composition comprising the bispecific antibody of claim 64 and a carrier.

Kostelny teaches bispecific F(ab')2 antibodies, which are antibodies that comprise a $C_H1$ domain as well as the hinge region of an antibody constant region. F(ab')2 antibodies comprise four polypeptides. Kostelny's bispecific antibodies further comprise Fos and Jun dimerization domains. Therefore, Kostelny teaches bispecific antibodies that are the same as that claimed.

10. Claims 64-66 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Carter (US 5,731,168; cited in the IDS).

Claim 64 is drawn to a bispecific antibody comprising four polypeptides wherein the first and the second of the polypeptides each comprises a heavy chain constant domain and a heavy chain variable domain. Claim 64 may be interpreted as including within its scope antibodies where the light chains are not identical (see 112, 2nd rejection above). The claims include within their scope bispecific antibodies having multimerization domains of the first and second polypeptide that interact at an amino acid side chain protuberance of one of the first and second polypeptides and an amino acid side chain cavity of the other polypeptide.

Carter teaches methods of making heteromultimers where the first and second polypeptide each comprise an antibody constant domain, and where in the antibody constant domain is a $C_H3$ domain (see column 53, claims 14 and 15 together with claim 1, column 51), and further that the heteromultimers meet at an interface that is preferably a $C_H3$ domain (see

column 11, line 63 – column 12, line 9). The $C_H3$ domains may be altered to comprise protuberances and cavities, or other alterations (see column 23, lines 7 – 64). Therefore, Carter teaches bispecific antibodies that are the same as that claimed.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 54, 55, 58-61 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March; cited in an IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS), in view of Carter (US Patent 5,731,168; issued Mar. 24, 1998; effective filing date Mar. 1, 1995; cited in an IDS).

Claims 54, 55, 58-61 and 63 include within their scope, bispecific antibodies that contain engineered $C_H3$ domains, where the first and second polypeptides interact at an amino acid side chain protuberance of one polypeptide and an amino acid side chain cavity of the other polypeptide. Although claim 59 describes the bispecific antibody as comprising elements "(a)", "(b)" and "(c)", claim 59 is interpreted to read on bispecific scFv antibodies because the claim does not make clear that the common light chain variable domain of element "(a)" is in a separate polypeptide from the first and second polypeptides of elements "(b)" and "(c)".

de Kruif teaches a method for making bispecific scFv antibodies containing regions of a constant comain and (IgG3 hinge regions) and either a Fos or Jun leucine zipper to the scFv proteins, where the light chain variable domains of the scFv antibodies are the same for each of the binding domains of the bispecific scFv. The nucleic acid encoding the dimerization regions (IgG3 together with the leucine zippers and cysteine residues) are dimerization cassettes that are introduced into the NotI restriction sites of genes encoding scFvs isolated from a variety of phage display libraries, such as that of Nissim (see page 7632, 2nd column of de Kruif). Merchant provides evidence that the library of Nissim is a library that has extensive H chain repertoires and unique L chain sequence. Thus, each antibody fragment derived from the phage library of Nissim has the same L chain (see page 677, 1st column), and a bispecific antibody

made by the method taught by de Kruif would inherently produce bispecific antibodies where each light chain was identical. de Kruif fails to teach dimerization cassettes (mulitimerization domains) that comprise a $C_H3$ domain of an antibody constant domain, or to teach engineered $C_H3$domains, where the first and second polypeptides interact at an amino acid side chain protuberance of one polypeptide and an amino acid side chain cavity of the other polypeptide.

However, other dimerization strategies exist in the prior art that could be used to make bispecific antibodies. Carter teaches methods of making heteromultimers where the first and second polypeptide each comprise an antibody constant domain, and where in the antibody constant domain is a $C_H3$ domain (see column 53, claims 14 and 15 together with claim 1, column 51), and further that the heteromultimers meet at an interface that is preferably a $C_H3$ domain (see column 11, line 63 – column 12, line 9). The $C_H3$ domains may be altered to comprise protuberances and cavities, or other alterations (see column 23, lines 7 – 64). Carter also teaches that methods of making bispecific antibodies that are full length (therefore would comprise at least a $C_H3$ domain of an antibody) may provide advantages if the antibodies are to be used therapeutically (see col. 3, lines 58-64). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody encompassed by the claims, where the first binding site of the bispecific antibody comprised a light chain that was identical to the light chain of the second binding site, and where the bispecific antibody comprised a $C_H3$ domain that was altered so that the first and second polypeptide interact at an amino acid side chain protuberance of one of the first and second polypeptides and an amino acid side chain cavity of the other polypeptide. One would have been motivated to combine the teachings of de Kruif with that of Carter because Carter

teaches the advantages of making bispecific antibodies that comprise constant domains such as the $C_H3$ domain.

12. Claims 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Carter (supra) and further in view of Greenwood (Greenwood, J. et al., Ther. Immunol., 1(5): 247-255, 1994).

The combination of de Kruif and Carter teach as set forth above. The combination fails to teach bispecific antibodies comprising a multimerization domain comprising a non-naturally occurring disulfide bond between the first and second multimerization domain, and also where the non-naturally occurring disulfide bond is between the $C_H3$ multimerization domains of the first and second polypeptide. However, Greenwood teaches a method for making antibody dimers, where the method for dimerizing the antibodies was to engineer a mutation of a serine residue to cysteine near the carboxy-terminal of the $C_H3$ domain (see abstract). Thus, Greenwood demonstrates that it was known in the art to use the insertion of a non-naturally occurring disulfide bond in the $C_H3$ region for the purpose of making antibody dimers. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combined the teachings of de Kruif, Carter and Greenwood to make a bispecific antibody that comprised a $C_H3$ multimerization domain having an engineered mutation of a serine residue to cysteine for the purpose of dimerizing antibodies, because Carter teaches the usefulness of a dimerization strategy that involves a $C_H3$ domain and Greenwood teaches a method for engineering $C_H3$ domains with a non-naturally occurring disulfide bond.

13. Claims 64-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter (US 5,731,168; cited in the IDS) in view of Greenwood (supra).

Claim 64 is drawn to a bispecific antibody comprising four polypeptides wherein the first and the second of the polypeptides each comprises a heavy chain constant domain and a heavy chain variable domain. Claim may be interpreted as including within its scope antibodies where the light chains are not identical (see 112, 2nd rejection above). The claims include within their scope bispecific antibodies having multimerization domains are $C_H3$ domains with a non-naturally occurring disulfide bond.

Carter teaches as set forth above. Carter fails to teach a bispecific antibodies comprising a multimerization domain comprising a non-naturally occurring disulfide bond between the first and second multimerization domain, and also where the non-naturally occurring disulfide bond is between the $C_H3$ multimerization domains of the first and second polypeptide. However, Greenwood teaches a method for making antibody dimers, where the method for dimerizing the antibodies was to engineer a mutation of a serine residue to cysteine near the carboxy-terminal of the $C_H3$ domain (see abstract). Thus, Greenwood demonstrates that it was known in the art to use the insertion of a non-naturally occurring disulfide bond in the $C_H3$ region for the purpose of making antibody dimers. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combined the teachings of Carter and Greenwood to make a bispecific antibody that comprised a $C_H3$ multimerization domain having an engineered mutation of a serine residue to cysteine for the purpose of dimerizing antibodies, because Carter teaches the usefulness of a dimerization strategy that involves a $C_H3$ domain and

Greenwood teaches a method for engineering $C_H3$ domains with a non-naturally occurring disulfide bond.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
September 27, 2007

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER